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14. ABSTRACT

Objective: Demonstrate occupational exposure to non-hypoxic hypobaria is associated with subcortical white matter hyperintensity (WMH) on fluid attenuated inversion recovery (FLAIR) magnetic resonance imaging (MRI).
Methods: Eighty-three altitude chamber personnel (PHY), 105 U-2 pilots (U2P), and 148 age- controlled and health-matched doctorate degree controls (DOC) underwent high-resolution MRI. Subcortical WMH burden was quantified as count and volume of subcortical WMH lesions after transformation of images to the Talairach-atlas-based stereotactic frame.
Results: Subcortical WMH are more prevalent in PHY (volume $p=0.011$/count $p=0.019$) and U2P (volume $p<0.001$/count $p<0.001$) when compared to DOC, while PHY are not significantly different than U2P.
Interpretation: This study provides strong evidence that non-hypoxic hypobaric exposure may induce subcortical WMH in a young, healthy population lacking other risk factors for WMH and adds this occupational exposure to other environmentally related potential causes of WMH.

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Hypobaria; magnetic resonance imaging; white matter hyperintensity

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White Matter Hyperintensities and Hypobaric Exposure

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Objective: Demonstrate that occupational exposure to nonhypoxic hypobaria is associated with subcortical white matter hyperintensities (WMHs) on fluid-attenuated inversion recovery magnetic resonance imaging (MRI).
Methods: Eighty-three altitude chamber personnel (PHY), 105 U-2 pilots (U2P), and 148 age- controlled and health-matched doctorate degree controls (DOC) underwent high-resolution MRI. Subcortical WMH burden was quantified as count and volume of subcortical WMH lesions after transformation of images to the Talairach atlas–based stereotactic frame.
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Decompression sickness (DCS), including neurological DCS (NDCS), is an occupational risk for high-altitude aviators and has been attributed to low ambient pressure (hypobaric) exposure. The clinical course is typically minor, but moderate to severe NDCS may cause permanent neurological injury.[1,2] We previously reported that exposure to nonhypoxic, hypobaric conditions in high-altitude U-2 pilots was associated with subcortical white matter hyperintensity (WMH) changes on T2-weighted images even in the absence of clinical symptoms when compared to matched controls.[3,4] A valid criticism of this work included the suggestion that other occupational factors, specifically "exposure to high G stress, radiation, or use of stimulant drugs," may have contributed to the increased incidence of WMH changes in military pilots.[5]

Here, we aimed to address this criticism by evaluating a group of individuals with occupational exposure to nonhypoxic hypobaria who lack exposure to these other potential risk factors. US Air Force (USAF) altitude chamber operations technicians are occupationally exposed to repetitive, monitored, nonhypoxic hypobaria when performing essential safety observation of aircrew undergoing hypoxic hypobaric awareness training. Similar to U-2 pilots, chamber technicians undergo pre-exposure nitrogen degassing with 100% O_2 delivered via an aviator mask. We hypothesized that occupational exposure to hypobaria in chamber technicians may lead to subcortical WMH changes similar to those observed in high-altitude pilots. We compared subcortical WMH burden in chamber technicians to that of high-altitude pilots with nonhypoxic hypobaric exposure and healthy controls with no occupational exposure. Previously, we observed no significant association between volume of periventricular WMH lesion and hypobaric exposure, and therefore all follow-up analyses concentrated on the subcortical WMHs.[4]

Subjects and Methods

Participants

The study was reviewed and approved by the Air Force Research Laboratory Institutional Review Board. All participants were active duty members of the US military recruited with strict adherence to Department of Defense requirements regarding protection of human subjects in research. Participation in this study was voluntary, and commanding officers were not involved in, or knowledgeable of, participation. All participants acknowledged this was not an anonymous study and provided informed consent prior to testing. Subjects did not receive compensation for participation, but subjects' travel costs were reimbursed as permitted under Federal Government travel regulations.

All participants were between the ages of 26 and 50 years, were healthy at time of study without any history of central neurologic or psychiatric disease, and had undergone a routine annual medical examination within 12 months prior to study. All participants at the time of testing met USAF Flying Class II neurological standards.[6] Briefly, exclusionary criteria for Flying Class II include a history of any of the following: head trauma with any loss of consciousness or amnesia; migraine headache; psychiatric or psychological disease requiring any medication or hospitalization; hypertension (HTN) requiring more than a single angiotensin-converting enzyme inhibitor (ACE-I) for control; hyperlipidemia (HLD) requiring more than a single statin for control; diabetes or glucose intolerance; ischemic cardiac disease; any neurological disease including infection, seizure, or stroke; any medical condition associated with neurological injury; or substance or drug abuse or dependence.

Study population sizes for altitude chamber operations personnel (PHY) and doctorate degree, healthy, age-controlled volunteers (DOC) were established based on the assumption of 5% difference among study populations. All active duty PHY were invited to participate, and we accepted the first 83 subjects who responded to our invitation and met study entry criteria. All PHY had experienced >50 occupational exposures to >25,000 feet altitude with duration of 30 to 60 minutes. Exposure frequency was variable but generally not more often than every third day, although occasionally mission demands required every other day exposure. All active duty USAF U-2 pilots (U2P) were invited to participate and 105 individuals agreed, exceeding a 90% participation rate.[4] U2P are exposed to hypobaric cabin altitudes (28,000–30,000 feet) for up to 9 hours with a variable frequency but not more often than every third day. For structural magnetic resonance imaging (MRI) comparison, 148 active duty DOC were recruited as previously described.[4] Two (2.4%) of PHY and 16 (15%) of U2P reported mission-related symptoms of NDCS. All U2P and PHY undergo standardized hypoxic hypobaric chamber exposure as part of routine aircrew qualification training every 5 years; these exposures are of 30- to 60-minute duration with hypoxia relieved via 100% oxygen aviator mask with the onset of physiological symptoms. Fourteen DOC have experienced a single episode of aircrew hypoxic hypobaric chamber exposure as part of initial flight surgeon qualification training. No subject experienced NDCS related to this periodic aircrew chamber training.

MRI Assessment

Structural MRI data for U2P were collected at the Research Imaging Institute, University of Texas Health Science Center, San Antonio, Texas, using a Siemens (Erlangen, Germany) 3T Tim Trio scanner equipped with a 12-channel phase array coil.[3] Structural MRI data for PHY and DOC were collected at the Wilford Hall Ambulatory Surgical Center, 59th Medical Wing, Lackland Air Force Base, Texas, using a Siemens 3T Verio scanner equipped with a 32-channel phase array coil.[4] Both scanners are operated under quality control and assurance guidelines in accordance with recommendations by the American College of Radiology, and cross-calibration between scanners was performed as previously described.[4] Briefly, 3-dimensional imaging parameters were for T1 magnetization prepared rapid acquisition gradient echo, repetition time (TR) = 2,200 milliseconds, echo time (TE) = 2.85 milliseconds, isotropic resolution = 0.80mm and for fluid-attenuated inversion recovery (FLAIR), TR = 4,500 milliseconds, TE = 311 milliseconds, isotropic resolution = 1.00mm. FLAIR images were coregistered to a common Talairach atlas–based stereotactic frame. An experienced neuroanatomist blinded to group as previously described manually traced WMHs,[4] and a neuroradiologist blinded to clinical history provided MRI interpretation. For each lobe we manually counted the number of WMHs (count) and used in-house software (P.V.K.) to compute the total volume of WMHs (volume).

Statistical Analysis

The volume, prevalence, and regional distribution of WMHs were compared among 3 groups: PHY, U2P, and DOC. Group-wise analyses of the difference in the WMH volume/count were performed using the 2-tailed nonparametric Mann–Whitney U test because the Shapiro–Wilk test indicated non-normal distribution in WMH volume and count measurements ($p < 0.001$ for all groups). In post hoc analysis, we utilized Student t test, demonstrating similar results with the same or smaller probability values in all analyses. Overall, the selected nonparametric tests were conservative in estimating the significance of the differences among populations. We utilized the Kolmogorov–Smirnov test for the equality of continuous 1-dimensional probability distribution for comparison of WMH volumes between PHY and U2P, testing similarity of volumes. We used the Jonckheere–Terpstra test for an ordered alternative hypothesis to evaluate DOC $\leq$ PHY $\leq$ U2P WMH volume/count.[7] Correlation of age and total hours of exposure to WMH volume/count was performed using the nonparametric Spearman rank correlation coefficient test. Additionally we utilized a linear regression analysis for the relationship of age or hours of exposure to WMH volume/count. U2P WMH volume/count were adjusted using the linear regression coefficients obtained from the calibration study to accommodate for the higher signal-to-noise ratio of the Wilford Hall Ambulatory Surgical Center imaging center as previously described.[4] We considered $p < 0.05$ as the threshold for significance.

Results

For DOC the mean age was 34.6 years, for PHY 36.5 years, and for U2P 37.7 years (Table 1). Mild HTN

TABLE 1. Correlation of WMH Volume and Count with Age and with Total High-Altitude Exposure Hours

Group	Statistical Measure[a]	WMH Vol		WMH Cnt	
		Spearman rho	Linear Regression r^2	Spearman rho	Linear Regression r^2
Age, yr, vs WMH Vol/Cnt					
DOC, n = 148	34.6/33.0/5.8/33.6–35.5	0.189	0.017	0.205	0.029
PHY, n = 83	36.5/36/7.1/34.5–37.5	0.084	0.023	0.018	0.003
U2P, n = 105	37.7/37.5/36.6–38.8	0.142	0.019	0.124	0.017
Exposure, h, vs WMH Vol/Cnt					
PHY, n = 83	97/73/88/78–116	−0.002	0.008	−0.065	0.015
U2P, n = 105	741/667/489/648–834	0.144	0.002	0.122	0.001
PHY+U2P, n = 188	461/219/491/391–531	0.141	0.002	0.095	0.009

[a]Mean/median/standard deviation/95% confidence interval.
Cnt = count; DOC = doctorate degree, healthy, age-controlled volunteers; PHY = altitude chamber operations personnel; U2P = U-2 pilots; Vol = volume; WMH = white matter hyperintensity.

controlled by a single ACE-I was present in 10 of 148 DOC, 7 of 83 PHY, and 8 of 105 U2P, and mild HLD controlled on a single statin was present in 6 of 148 DOC, 4 of 83 PHY, and 14 of 105 U2P. Either HTN or HLD was present in 14 of 148 DOC, 10 of 83 PHY, and 20 of 105 U2P, and both were present in 2 of 148 DOC, 1 of 83 PHY, and 2 of 105 U2P.

Group-wise analysis demonstrated that both PHY and U2P had significantly elevated WMH volume/count compared to DOC (Table 2). Although the WMH volume/count were higher in U2P than in PHY, neither was statistically significant. Comparable results were obtained in group-wise analysis after excluding any subject with HTN or HLD and after excluding PHY or U2P who had experienced NDCS. Equivalency of U2P to PHY WMH volume was noted on the Kolmogorov–Smirnov test ($p = 0.388$). The Jonckheere–Terpstra test demonstrated DOC < PHY ≤ U2P on WMH volume ($p = 0.024$) and count ($p = 0.012$); PHY < U2P was not significant ($p > 0.10$).

The Spearman correlation coefficients between WMH volume/count and age and hours of hypobaric exposure were positive but not significant (see Table 1). Linear regression of combined PHY and U2P total hours of hypobaric exposure versus WMH volume/count was not significant (WMH volume/count, $r^2 = 0.002/r^2 = 0.009$, respectively). The total hours of exposure were not significantly associated with WMH presence in either group (Fig 1). Likewise, the Spearman correlation

coefficient between 2 measures of WMH burden and age were positive but not significant (all $r^2 < 0.03$; all $p > 0.10$). Stratifying subjects into 5-year age intervals demonstrated significant differences between the 2 groups exposed to hypobaria and controls for the youngest stratum (26–30 years; PHY+U2P compared to DOC WMH volume/count, $p = 0.051/0.027$, respectively). The WMH burden remained elevated for combined PHY and U2P across all age categories, but the group difference was not significant in other age strata (Fig 2).

The distribution of WMH volume/count per lobe demonstrated an increase, with DOC < PHY ≤ U2P. In addition, confidence intervals for total subcortical WMH volume/count and for frontal lobe WMH volume/count did not overlap when comparing DOC and PHY or DOC and U2P, whereas confidence intervals did overlap for PHY and U2P. For the other lobes, although there was a trend toward absolute value increase from DOC to PHY to U2P, there was also overlap of confidence intervals, reflecting the small values (Fig 3).

Discussion

WMHs are nonspecific findings on MRI associated with normal aging, multiple neurological conditions,[8–11] and environmental factors such as traumatic brain injury.[12] Importantly, our study demonstrated a significant WMH burden increase in 2 groups (PHY and U2P) occupationally exposed to nonhypoxic hypobaria compared to age-controlled and health-matched controls not explained by

TABLE 2. Mean WMH Volume and Count by Group[a]

WMH	DOC, Mean ± SD (CI)	PHY, Mean ± SD (CI)	U2P, Mean ± SD (CI)	Mann–Whitney–Wilcoxon Significance, 2-Tailed		
				DOC:PHY	DOC:U2P	U2P:PHY
All subjects	n = 148	n = 83	n = 105			
Volume, ml	0.032 ± 0.058 (0.022–0.042)	0.126 ± 0.404 (0.040–0.212)	0.147 ± 0.296 (0.090–0.204)	$p = 0.011$	$p < 0.001$	$p = 0.237$
Count	2.6 ± 3.1 (2.1–3.1)	6.4 ± 11.1 (4.0–8.8)	9.7 ± 18.3 (6.2–13.2)	$p = 0.019$	$p < 0.001$	$p = 0.091$
All minus HTN/HLD	n = 132	n = 73	n = 85			
Volume, ml	0.033 ± 0.060 (0.023–0.043)	0.130 ± 0.428 (0.032–0.228)	0.114 ± 0.208 (0. 070–0.158)	$p = 0.045$	$p = 0.003$	$p = 0.397$
Count	2.6 ± 3.1 (2.1–3.1)	6.3 ± 11.5 (3.7–9.0)	7.4 ± 12.7 (4.7–10.1)	$p = 0.068$	$p < 0.001$	$p = 0.235$
All minus NDCS	n = 148	n = 81	n = 83			
Volume, ml	0.032 ± 0.058 (0.022–0.042)	0.126 ± 0.409 (0.038–0.214)	0.134 ± 0.303 (0.069–0.199)	$p = 0.039$	$p = 0.003$	$p = 0.404$
Count	2.6 ± 3.1 (2.1–3.1)	6.2 ± 11.1 (3.8–8.7)	9.2 ± 18.6 (5.2–13.2)	$p = 0.064$	$p < 0.001$	$p = 0.106$

[a]All subjects; all subjects after exclusion of HTN or HLD; all subjects after exclusion of clinical NDCS.
CI = confidence interval; DOC = doctorate degree, healthy, age-controlled volunteers; HLD = hyperlipidemia; HTN = hypertension; NDCS = neurological decompression sickness; PHY = altitude chamber operations personnel; SD = standard deviation; U2P = U-2 pilots; WMH = white matter hyperintensity.
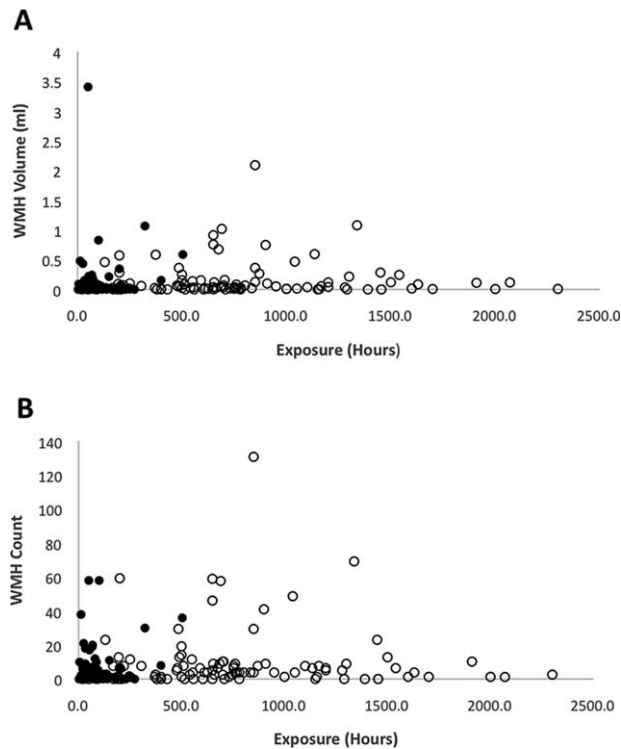
A

B

FIGURE 1: Distribution of individual subjects displaying (A) white matter hyperintensity (WMH) volume and (B) WMH count versus total hours of hypobaric exposure. Open circles = U-2 pilots; solid circles = altitude chamber operations personnel.

age alone. These findings persist even when we excluded any subject with HTN, HLD, or NDCS. Both populations are occupationally exposed to nonhypoxic hypobaria >25,000 feet (7,620m, 5.45 pounds per square inch absolute, 37.6kPa) following pre-exposure nitrogen degassing with 100% oxygen, and both populations are maintained on 100% oxygen throughout the hypobaric exposure. When clinical symptoms did occur, no equipment failures or procedural lapses were identified. Although U2P may have other potential environmental risks for developing WMH including exposure to radiation and varying G-force, PHY hypobaric exposure occurs in ground-based altitude chambers under controlled conditions without the presence of these other associated factors. Although both PHY and U2P undergo routine hypoxic hypobaric aircrew training, this represents only a small fraction of their hypobaric exposure and is unlikely to have contributed to our findings. The finding of elevated WMH and the pattern of WHM burden in both groups argues for a similarity of pathophysiological factors and suggests that the nonhypoxic hypobaric exposure experience is the likely causative factor. Furthermore, the progressive rise in the WMH volume and count from DOC to PHY to U2P suggests that an increase in exposure intensity and/or duration may have a cumulative effect on the WMH burden.

Although the group differences between PHY and U2P did not reach statistical significance, the PHY WMH values were less than those of U2P on 7 of 9 groupings, suggesting that an increase in sample size would likely lead to a demonstrable significant difference. The largest group differences in WMH burden were observed in the youngest subjects (age 26–30 years), where WMH burden is expected to be minimal, again arguing for hypobaric exposure as the causative factor. Although the relative values in PHY versus U2P vary, this may reflect small sampling size, difference in exposure intensities at various career times, improvement in WMH burden over time, or other unknown factors. This will be further addressed by regular MRI follow-up instituted for USAF U2P pilots

The relationship between hypobaric exposure and WMH is complex. We observed no significant correlations between WMH measurements and the total number or hours of hypobaric exposure. This suggests that other factors may modulate the hypobaria-related WMH change, including hyperoxemic pre-exposure nitrogen degassing, exposure duration, level of physical and mental activity during exposure, frequency of exposure episodes, and amount of rest between exposures, as well as other yet unknown environmental and genetic susceptibility risk factors.
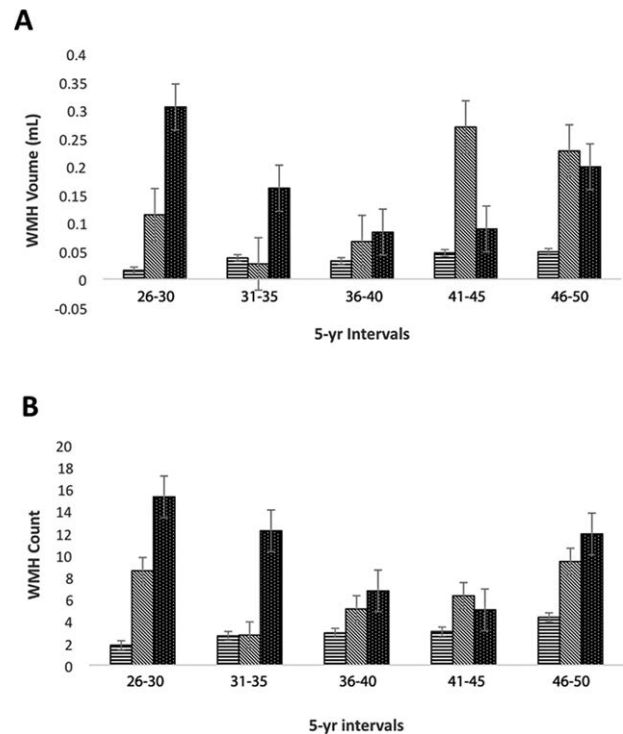
A

B

FIGURE 2: Comparison of (A) white matter hyperintensity (WMH) volume and (B) WMH count per 5-year interval for the ages 26 to 50 years by group. Horizontal stripes = doctorate degree, healthy, age-controlled volunteers; diagonal stripes = altitude chamber operations personnel; dots = U-2 pilots. Mean values are given with standard error.
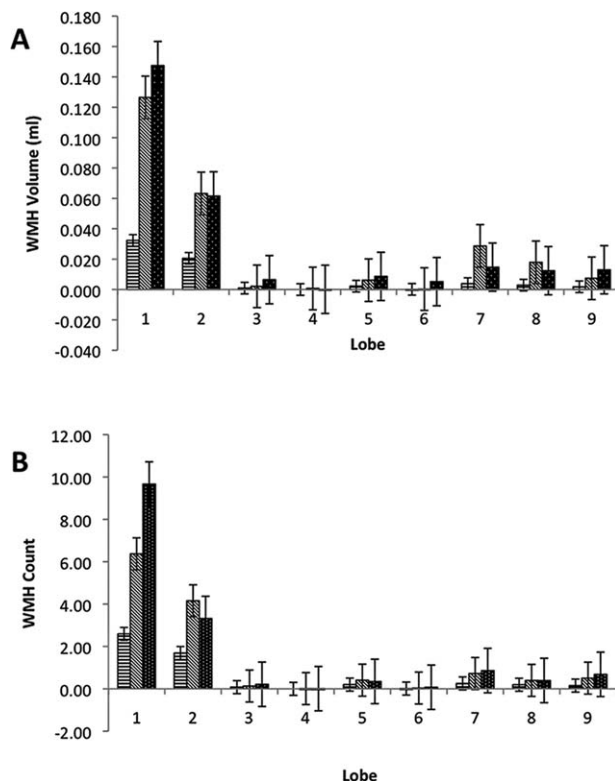
FIGURE 3: Comparison of (A) white matter hyperintensity (WMH) volume and (B) WMH count per lobe by group. Horizontal stripes = doctorate degree, healthy, age-controlled volunteers; diagonal stripes = altitude chamber operations personnel; dots = U-2 pilots. Mean values are given with standard error. 1 = total; 2 = frontal; 3 = insular; 4 = interhemispheric; 5 = limbic; 6 = occipital; 7 = parietal; 8 = sublobar; 9 = temporal.

WMH burden is a marker of cerebral integrity[8] that is associated with cognitive decline, particularly in domains of executive functioning,[13] processing speed, and general cognitive status.[14] In agreement with this, U2P demonstrated lower neurocognitive performance scores but not clinical impairment in the domains of reasoning/calculation, memory, information-processing accuracy, and general cognitive functioning when compared to USAF pilot controls not routinely exposed to repetitive hypobaria.[15] Furthermore, within U2P, the lower neurocognitive performance scores were significantly correlated with WMH burden. The correlations between lower neurocognitive scores and higher WMH burden observed in U2P are similar to previous reports associating WMH burden with performance in elderly populations with medical risk factors.[16,17] This suggests that WMH burden likely produced by environmental factors may have a measurable neurocognitive impact in a population that is free of cardiovascular, cerebrovascular, and other genetic risk factors posited as the culprits of neurocognitive decline in aging and other disorders. Clinical neurocognitive impairment has not been demonstrated in

U2P personnel, most likely due to a higher intrinsic cognitive reserve in these highly functioning healthy individuals with advanced education.[18]

The pathophysiological mechanisms underlying the rise in WMH burden due to hypobaric exposure are unknown. We previously hypothesized that WMH lesions may be caused by microemboli ($<30\mu m$) originating in blood from exposure to hypobaria, with the distribution of WMH volume roughly paralleling lobe volume in U2P.[4] Supporting this hypothesis is the distribution of microemboli measured by ultrasound, with 70% in the middle cerebral artery distribution and 30% in the anterior cerebral artery distribution.[19] Observing a similar distribution pattern in the PHY as seen in U2P provides additional support for this hypothesis. Unknown is whether these microemboli are nitrogen microbubbles, platelet/thrombin aggregates, or microparticles and/or proinflammatory leukocytes. The randomness of this mechanism would explain the distribution of WMH in U2P and PHY compared to controls.[4]

An alternate hypothesis is the activation of a neuroinflammatory response following a regional nonocclusive ischemic episode and/or intracellular ischemia despite the maintenance of arterial normoxemia. The initial insult may be axonal, glial, or cytotoxic followed by activation of neuroinflammatory responses. Chronic upregulation of innate immune pathways is associated with reduced white matter integrity in healthy aging individuals.[20] It causes the release of proinflammatory factors, the activation of the multiprotein oligomer inflammasome, and the recruitment of immune cells. This response is neuroprotective in cases of exogenous pathogens.[21,22] However, chronic activation of immune pathways by endogenous factors, such as amyloid-beta peptide, may lead to neurodegeneration.[22,23] Occupational hypobaric exposure may therefore cause oversensitization of the innate immune pathways, triggering an inflammatory reaction that is followed by associated extracellular/intracellular fluid shift detectable as WMHs. Whether this inflammatory reaction is self-limited or predisposes to ongoing further injury with upregulation of the innate neuroinflammatory response is unknown.

Elevated WMH burden was present in the 2 groups with recurrent occupational exposure to nonhypoxic hypobaria, high-altitude U-2 pilots and altitude chamber physiology personnel, when compared to age-controlled and health-matched controls. There were no significant differences in the aging-related elevation in the subcortical WMH volume among the 3 groups. These aging trends were not statistically significant ($p > 0.10$) and were similar to aging trends previously reported in a large Hispanic sample aged 26 to 50 years.[24] This

suggests that the observed group differences in WMH burden are likely to be produced by causes other than chronic aging disorders. Therefore, this study provides strong evidence that exposure to nonhypoxic hypobaric conditions following hyperoxemic nitrogen degassing may induce subcortical WMH change, thus identifying hypobaria as an environmental risk factor for subcortical WMH burden in a healthy population of young adults free of typical cardiovascular and cerebrovascular risk factors. The underlying pathophysiology for hypobaria-associated WMH burden and whether this is similar to other environmental factors such as concussive brain injury are unknown. The implications of this increased WMH burden to long-term cerebral and cognitive health are also unknown but are of concern given reduced neurocognitive test performance associated with WMH burden in U2P. Also of concern is the possibility that repetitive stimulation of the immune response may lead to oversensitization of immune pathways, contributing to neurodegeneration in healthy individuals.[21] Presently, hypobaric-induced clinical neurological symptoms are treated with compression in hyperbaric units, but whether other therapies, including those addressing neuroinflammatory mechanisms, would be effective is unknown and warrants further study. Finally, our study clearly demonstrates this WMH burden occurs in the absence of clinical symptoms of hypobaria, suggesting reliance solely on clinical symptoms is inadequate for assessment of injury and thus advocating a need for more effective preventative and/or postexposure intervention.

Authorship

S.A.M. and P.V.K. conceived and designed the study, collected and analyzed data, and wrote the manuscript. P.M.S. designed the study, collected and analyzed data, and edited the manuscript. S.A.W., L.M.R., P.M.G., J.H.S., and A.Y.R. designed the study, analyzed data, and edited the manuscript.

Potential Conflicts of Interest

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